

Amendments to the Specification

Please replace the paragraph beginning at line 9 on page 5 with the following amended paragraph:

Using the method of Benight et al. a family of 100 sequences was obtained using a computer algorithm to have optimal hybridization properties for use in nucleic acid detection assays. The sequence set of 100 oligonucleotides was characterized in hybridization assays, demonstrating the ability of family members to correctly hybridize to their complementary sequences with an absence of cross hybridization. These are the sequences having SEQ ID NOs: ~~1 to 100~~ 1173 to 1272 of Table I. This set of sequences has been expanded to include an additional 110 sequences that can be grouped with the original 100 sequences as having non-cross hybridizing properties, based on the characteristics of the original set of 100 sequences. These additional sequences are identified as SEQ ID NOs: ~~101 to 210~~ 1273 to 1382 of the sequences in Table I. How these sequences were obtained is described below.

Please replace the paragraph beginning at line 10 on page 12 with the following amended paragraph:

A phantom sequence may thus be generated from exemplary Sequence 1 and Sequence 2 as follows:

Sequence 1: ATGTTTAGTGAAAAGTTAGTATTG (SEQ ID NO:1383)

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Sequence 2: ATGTTAGTGAATAGTATAGTATTG (SEQ ID NO:1384)

 • ♦

Phantom Sequence: ATGTTAGTGAAAGTTAGTATTG

Please replace the paragraph beginning at line 32 on page 53 with the following amended paragraph:

A preferred family of 100 tags is shown as SEQ ID NOS: ~~1 to 100~~ 1173 to 1272 in Table I. Characterization of the family of 100 sequence tags was performed to determine the ability of these sequences to form specific duplex structures with their complementary sequences and to assess the potential for cross hybridization. The 100 sequences were synthesized and spotted onto glass slides where they were coupled to the surface by amine linkage. Complementary tag sequences were Cy3-labeled and hybridized individually to the array containing the family of 100 sequence tags. Formation of duplex structures was detected and quantified for each of the positions on the array. Each of the tag sequences performed as expected, that is the perfect match duplex was formed in the absence of significant cross hybridization under stringent hybridization conditions. The results of a sample hybridization are shown in Figure 1. Figure 1a shows the hybridization pattern seen when a microarray containing all 100 probes was hybridized with the target complementary to probe 181234. The 4 sets of paired spots correspond to the probe complementary to the target. Figure 1b shows the pattern seen when a similar array was hybridized with a mix of all 100 targets. These results indicate that the family of sequences which is the subject of this patent can be used as a family of non-cross hybridizing (tag) sequences.

Please replace the paragraph beginning at line 16 on page 54 with the following amended paragraph:

The family of 100 non-cross-hybridizing sequences can be expanded by incorporating additional tetramer sequences that are used in constructing further 24mer oligonucleotides. In one example, four additional words were included in the generation of new sequences to be considered for inclusion as non-cross talkers in a family of sequences that were obtained from the above method using 10 tetramers. In this case, the four additional words were selected to avoid potential homologies with all potential combinations of other words: YYXW (TTAG); WYYX (GTTA); XYXW (ATAG) and WYYY (GTTT). The total number of sequences containing six words using the 14 possible words is 14^6 or 7,529,536. These sequences were screened to eliminate sequences that contain repetitive regions that present potential hybridization problems such as four or more of a similar base (e.g., AAAA or TTTT) or pairs of G's. Each of these sequences was compared to the sequence set of the original family of 100 non-cross-hybridizing sequences (SEQ ID NOs: ~~1 to 100~~ 1173 to 1272). Any new sequence that contained a minimal threshold of homology (that does not include the use of insertions or deletions) such as 15 or more matches with any of the original family of sequences was eliminated. In other words, if it was possible to align a new sequence with one or more of the original 100 sequences so as to obtain a maximum simple homology of 15/24 or more, the new sequence was dropped. Simple homology" between a pair of sequences is defined here as the number of pairs of nucleotides that are matching (are the same as each other) in a comparison of two aligned sequences divided by the total number of potential matches. "Maximum simple homology" is obtained when two sequences are aligned with each other so as to have the maximum number of paired matching nucleotides. In any event, the set of new sequences so obtained was referred to as the "candidate sequences". One of the candidate sequences was arbitrarily chosen and referred to as sequence 101. All the candidate sequences were checked against sequence 101, and sequences that contained 15 or more non-consecutive matches (i.e., a maximum simple homology of 15/24 (62.5%) or more were

eliminated. This results in a smaller set of candidate sequences from which another sequence is selected that is now referred to as sequence 102. The smaller set of candidate sequences is now compared to sequence 102 eliminating sequences that contained 15 or more non-consecutive matches and the process is repeated until there are no candidate sequences remaining. Also, any sequence selected from the candidate sequences is eliminated if it has 13 or more consecutive matches with any other previously selected candidate sequence.

Please replace the paragraph beginning at lines 15 and 23 on page 55 with the following amended paragraphs, respectively:

The additional set of 73 tag sequences so obtained (SEQ ID NOS:~~101 to 173~~ 1273 to 1345 of Table 1) is composed of sequences that when compared to any of SEQ ID NOS:~~1 to 100~~ 1173 to 1272 of Table I have no greater similarity than the sequences of the original 100 sequence tags of Table I. The sequence set as derived from the original family of non cross hybridizing sequences, SEQ ID NOS:~~1 to 173~~ 1173 to 1345 of Table 1, are expected to behave with similar hybridization properties to the sequences having SEQ ID NOS:~~1 to 100~~ 1173 to 1272 since it is understood that sequence similarity correlates directly with cross hybridization (Southern et al., Nat. Genet.; 21, 5-9: 1999).

The set of 173 24mer oligonucleotides were expanded to include those having SEQ ID NOS:~~174 to 210~~ 1346 to 1382 as follows. The 4mers WXYW, XYXW, WXXW, WYYW, XYYX, YXYX, YXXY and XYXY where W=G, X=A, and Y=U/T were used in combination with the fourteen 4mers used in the generation of SEQ ID NOS:~~1 to 173~~ 1173 to 1345 to generate potential 24-base oligonucleotides. Excluded from the set were those containing the sequence patterns GG, AAAA and TTTT. To be included in the set of additional 24mers, a sequence also had to have at least one of the 4mers containing two G's: WXYW (GATG), WYXW (GTAG), WXXW (GAAG), WYYW (GTTG) while also containing exactly six G's. Also

required for a 24mer to be included was that there be at most six bases between every neighboring pair of G's. Another way of putting this is that there are at most six non-G's between any two G's. Also, each G nearest the 5'-end of its oligonucleotide (the left-hand side as written in Table I) was required to occupy one of the first to seventh positions (counting the 5'- terminal position as the first position.) A set of candidate sequences was obtained by eliminating any new sequence that was found to have a maximum simple homology of 16/24 or more with any of the previous set of 173 oligonucleotides (Table 1, SEQ ID NOs:~~1 to 173~~ 1173 to 1345). As above, an arbitrary 174th sequence was chosen and candidate sequences eliminated by comparison therewith. In this case the permitted maximum degree of simple homology was 16/24. A second sequence was also eliminated if there were ten consecutive matches between the two (i.e., it was notionally possible to generate a phantom sequence containing a sequence of 10 bases that is identical to a sequence in each of the sequences being compared). A second sequence was also eliminated if it was possible to generate a phantom sequence 20 bases in length or greater.

Please replace the paragraphs beginning at lines 1 and 4 on page 57 with the following amended paragraphs, respectively:

The selection of sequences using this approach would be amenable to a computerized process. Thus for example, a string of 10 contiguous bases of the first 24mer of Table I could be selected: GATTGTATTGATTGAGATTAAAG (SEQ ID NO:1173).

A string of contiguous bases from the second 24mer could then be selected and compared for maximum homology against the first chosen sequence: TGATTGTAGTATGTATTGATAAAG (SEQ ID NO:1174).

Please replace the paragraph beginning at line 1 on page 64 with the following amended paragraph:

A practical example of the aforementioned description is as follows:
For exon 1 of the human p53 tumor suppressor gene sequence the
following tag-Reverse primer (SEQ ID NO:1171) was generated:

222087

222063

5'-PO4-GATTGTAAGATTTGATAAAGTGTA-TCCAGGGAAGCGTGTCACCGTCGT-3'

Tag Sequence # 3

Exon 1 Reverse

The numbering above the Exon-1 reverse primer represents the genomic
nucleotide positions of the indicated bases.

The corresponding Exon-1 Forward primer sequence (SEQ ID NO:1172) is
as follows:

221873

221896

5'-Biotin-TCATGGCGACTGTCCAGCTTTGTG-3'

Please replace Table 1 beginning on page 87 with the following amended Table 1.

	SEQ ID NO (1)	Sequence	No Assigned in Example 3
1	<u>1173</u>	GATTTGTATTGATTGAGATTAAAG	1
2	<u>1174</u>	TGATTGTAGTATGTATTGATAAAG	2
3	<u>1175</u>	GATTGTAAGATTTGATAAAGTGTA	3
4	<u>1176</u>	GATTTGAAGATTATTGGTAATGTA	4
5	<u>1177</u>	GATTGATTATTGTGATTTGAATTG	5
6	<u>1178</u>	GATTTGATTGTAAAAGATTGTTGA	6
7	<u>1179</u>	ATTGGTAAATTGGTAAATGAATTG	7
8	<u>1180</u>	ATTGGATTTGATAAAGGTAAATGA	
9	<u>1181</u>	GTAAGTAATGAATGTAAAAGGATT	8
10	<u>1182</u>	GATTGATTGATTGATTGATTGAT	
11	<u>1183</u>	TGATGATTAAAGAAAGTGATTGAT	
12	<u>1184</u>	AAAGGATTTGATTGATAAAGTGAT	
13	<u>1185</u>	TGTAGATTTGTATGTATGTATGAT	10
14	<u>1186</u>	GATTTGATAAAGAAAGGATTGATT	
15	<u>1187</u>	GATTAAAGTGATTGATGATTTGTA	11
16	<u>1188</u>	AAAGAAAGAAAGAAAGAAAGTGTA	12
17	<u>1189</u>	TGTAAAAGGATTGATTTGTATGTA	
18	<u>1190</u>	AAAGTGTAGATTGATTAAAGAAAG	
19	<u>1191</u>	AAAGTTGATTGATTGAAAAGGTAT	
20	<u>1192</u>	TTGATTGAGATTGATTTTGAGTAT	
21	<u>1193</u>	TGAATTGATGAATGAATGAAGTAT	15
22	<u>1194</u>	GTAATGAAGTATGTATGTAAGTAA	

SEQ ID NO (1)	Sequence	No Assigned in Example 3
23	1195 TGATGATTTGAATGAAGATTGATT	16
24	1196 TGATAAAGTGATAAAGGATTAAAG	17
25	1197 TGATTTGAGTATTTGAGATTTTGA	18
26	1198 TGTAGTAAGATTGATTAAAGGTAA	
27	1199 GTATAAAGGATTGATTTTGAAAAG	
28	1200 GTATTTGAGTAAGTAATTGATTGA	19
29	1201 GTAAAAAGTTGAGTATTGAAAAAG	
30	1202 GATTTGATAAAGGATTTGTATTGA	
31	1203 GATTGTATTGAAGTATTGTAAAAG	20
32	1204 TGATGATTTTGATGAAAAAGTTGA	
33	1205 TGATTTGAGATTAAAGAAAGGATT	21
34	1206 TGATTGAATTGAGTAAAAAGGATT	22
35	1207 AAAGTGATAAAGGATTTGATGTAT	
36	1208 AAAGGTATTTGAGATTTGATTGAA	
37	1209 AAAGTTGAGATTTGAATGATTGAA	23
38	1210 TGTATTGAAAAGGTATGATTTGAA	
39	1211 GTATTGTATTGAAAAGGTAATTGA	24
40	1212 TTGAGTAATGATAAAGTGAAGATT	
41	1213 TGAAGATTTGAAGTAATTGAAAAG	25
42	1214 TGAAAAAGTGTAGATTTTGAGTAA	26
43	1215 TGTATGAATGAAGATTTGATTGTA	
44	1216 AAAGTTGAGTATTGATTTGAAAAG	27
45	1217 GATTTGTAGATTTGTATTGAGATT	
46	1218 AAAGAAAGGATTTGTAGTAAGATT	29
47	1219 GTAAAAAGAAAGGTATAAAGGTAA	30
48	1220 GATTAAAGTTGATTGAAAAGTGAA	31
49	1221 TGAAAAAGGTAATTGATGTATGAA	
50	1222 AAAGGATTAAAGTGAAGTAATTGA	33
51	1223 ATGAATTGGTATGTATATGAATGA	34
52	1224 TGAAATGAATGAATGATGAAATTG	35
53	1225 ATTGATTGTGAATGAAATGAATTG	36
54	1226 ATTGAAAGATGAAAAGATGAAAAG	37
55	1227 ATTGTTGAAAAGTGTAATGATTGA	38
56	1228 ATGATGTAATGAAAAGATTGTGTA	39
57	1229 AAAGATTGAAAGATGATGTAATTG	
58	1230 ATTGATGAGTATATTGTGTAGTAA	41
59	1231 AAAGATTGTGTAATTGATGATGAA	
60	1232 AAAGGTATATTGTGTAATGAGTAA	
61	1233 TGTAATGAGTATTGTAATTGAAAG	43
62	1234 GTATAAAGAAAGATTGGTAAATGA	44
63	1235 TTGAGTAATTGAATTGTGAAATGA	45
64	1236 TGTATTGAATGAATTGTTGATGTA	46
65	1237 TGTAATTGGTAAATGAGTAAAAAG	
66	1238 TGAATGAAATTGATGAGTATAAAG	
67	1239 GTAAGTAAATTGAAAGATTGATGA	49
68	1240 GTAAATGATGATATTGGTATATTG	50
69	1241 ATTGTTGATGATTGATTGAAATGA	51
70	1242 ATTGTGAAGTATAAAGATGATTGA	52
71	1243 ATGAAAAGTTGAGTAAATTGTGAT	
72	1244 ATGAATTGAAAGTGATTGAAAAAG	54
73	1245 GTAAATTGATGAAAAGTTGATGAT	
74	1246 AAAGTGATGTATATGAGTAAATTG	56
75	1247 GTAATGATAAAGATGATGATATTG	57

SEQ ID NO (1)	Sequence	No Assigned in Example 3
76	1248	TTGAAAAGATTGGTAATGATATGA
77	1249	AAAGTGAAAAAGATTGATTGATGA
78	1250	ATTGATGAGATTGATTATTGTGTA
79	1251	ATGAGATTATTGGATTTGTAGATT
80	1252	TGAAGATTATGAATTGGTAAGATT
81	1253	ATTGGATTATGAGATTATGATTGA
82	1254	ATTGTTGAATTGGATTAAAGATGA
83	1255	AAAGATGAGTAAGTAAATTGGATT
84	1256	AAAGGTAAGATTATTGATGAAAAG
85	1257	ATTGATGAGATTAAAGTTGAATTG
86	1258	GATTATTGGATTATGAAAAGGATT
87	1259	GATTTGTAATTGTTGAGTAAATGA
88	1260	AAAGAAAGATTGTTGAGATTATGA
89	1261	GTATAAAGGATTTTGAATTGATGA
90	1262	TTGAGATTGTAAATGAATTGTTGA
91	1263	GTATATTGATTGTGTGAATGAAAAG
92	1264	TGATATGAATTGGATTATTGGTAT
93	1265	ATGAATGATGAATGATGATTATTG
94	1266	ATGAATTGATTGGATTGTAATGAT
95	1267	GATTGTAATTGAGTAAATTGATGA
96	1268	GATTATTGGATTAAAGGTAAATGA
97	1269	ATTGTTGAATTGATGAGATTTGAT
98	1270	GATTATGAGTAAATTGATTGTGAT
99	1271	GATTATTGTTGATGAATGATATTG
100	1272	TGTAAAAGATTGAAAGGTATGATT
101	1273	GTATTTAGATGAGTTTGTAGATT
102	1274	TGAAGTTATGTAATAGAAAAGTGAT
103	1275	GTATGTATTGTATGTAGTTAATTG
104	1276	TGATATAGATAGTTAGATAGATAG
105	1277	ATGATGATGTATTGTAGTTATGAA
106	1278	TTAGTGAATGTATTAGTTGATGTA
107	1279	GTTAGTTAGATTATTGTTAGTTAG
108	1280	GTTAATTGTGTAGTTTGTATTGA
109	1281	GTTATGAAATAGTGATATTGTTAG
110	1282	ATTGTTAGAAAAGTGTAGATTAAAG
111	1283	ATGAGTATGTTATTAGTGTATGTA
112	1284	TGTAATAGTGAAGTTAGATTGTAT
113	1285	ATTGATAGATGATTAGTTAGTTGA
114	1286	ATGAGTTTGTATTATGAGATTAAAG
115	1287	TGATGTTTGATTATGATGTAGTAT
116	1288	ATGAGTTAGTTATGAATTAGATGA
117	1289	ATTGTTAGTGATGTTAGTAATTAG
118	1290	TGATGTAAGTATTGATGTTAGTTT
119	1291	GATTGTAAATAGAAAAGTGAAGTAA
120	1292	ATTGTGTATGAAGTATTGTATGAT
121	1293	ATAGTGATGTTATGAAGATTGTTA
122	1294	TTAGATGAATTGTGAAGTATTTAG
123	1295	GTAAGTTATGATTGATGTTATGAA
124	1296	GTATTGATGTTTAAAGTGTAAATAG
125	1297	GATTGTAAAGTAAGATTGTATATTG
126	1298	GTTTGTATTTAGATGAATAGAAAG
127	1299	GTTTGATTTGTAATAGTGATTGTA
128	1300	TGTATGTAGTATTTAGAAAGATGA

SEQ ID NO(1)	Sequence	No Assigned in Example 3
129	1301	ATGAATTGTGATAAAGAAAGTTAG
130	1302	TTAGTGTAGTAAGTTTAAAGTGTA
131	1303	GTATGATTGTTTGTAAATTAGTGAT
132	1304	GTTTAAAGTTAGTTGAGTTAGTAT
133	1305	ATAGTGTATGTAGATTATGAGATT
134	1306	TTGAATGATTAGTTGAGTATGATT
135	1307	GTATGTAAGTTAGTATGATTTGAA
136	1308	TGTAGTATATTGTTGAATTGTGAT
137	1309	ATAGTGATTGTATGTATGATAAAG
138	1310	TTAGTGATTGTATGTATATTGAAAG
139	1311	GTAAGATTATGAGTTATGATGTAA
140	1312	GTTATGAAATTGTTAGTGTAGATT
141	1313	GTTAGATTGTAGTTTAAAGATAG
142	1314	TTAGTGATTGAAATGATGTAGATT
143	1315	AAAGTGTAGTTATTAGTTAGTTAG
144	1316	AAAGAAAGTGTATGATGTTATTAG
145	1317	GATTGTATATTGTGTATGATGATT
146	1318	TTGAGATTGTTATGATATGAGTAT
147	1319	ATGAGTATGATTGTTATGATGTTT
148	1320	TGATTTAGTGAAATTGTGTATTAG
149	1321	TGAATGTATGTAGTATGTTTGTTA
150	1322	GTTAGTATTGATGATTATGAGTTA
151	1323	GTATATTGTGATTTAGTTGAGATT
152	1324	GTTAGTTTAAAGTTGAGATTGTTT
153	1325	GTATATTGTTAGATGAGATTTGTA
154	1326	TGATGTATGTTAGTTTATGAATGA
155	1327	TGTAGTATGTAATGTAGTATTTGA
156	1328	ATGAGTTATGTATTGAGTTAGTAT
157	1329	TGTATGATGATTATAGTTGAGTAA
158	1330	ATTGATGAATGAGTTTGTATAAAG
159	1331	TTGAGTTTATGATTAGAAAGAAAG
160	1332	TGATATTGATGAGTTAGTATTGAA
161	1333	ATAGAAAGTGAAATGAGTATGTTA
162	1334	TTGATGTAGATTGTATGTATATAG
163	1335	TTGAGATTATAGTGTAGTTTATAG
164	1336	TGATGTTAGATTGTTTGATTATTG
165	1337	TGTATTAGATAGTGATTGGAATGA
166	1338	GATTATGATGAATGTAGTATGTAA
167	1339	TGAATGATTGATATGAATAGTGTA
168	1340	GTAATGATTTAGTGTATTGAGTTT
169	1341	TGTAGTAATGATTGATGATAAAG
170	1342	TGAAGATTGTTATTAGTGATATTG
171	1343	GTATTTGAATGATGTAATAGTGTA
172	1344	GTATATGATGTATTAGATTGAAAG
173	1345	AAAGTTAGATTGAAAGTGATAAAG
174	1346	GTAAGATGTTGATATAGAAGATTA
175	1347	TAATATGAGATGAAAGTGAATTAG
176	1348	TTAGTGAAGAAGTATAGTTTATTG
177	1349	GTAGTTGAGAAGATAGTAATTAAT
178	1350	ATGAGATGATATTTGAGAAGTAAT
179	1351	GATGTGAAGAAGATGAATATATAT
180	1352	AAAGTATAGTAAGATGTATAGTAG
181	1353	GAAGTAATATGAGTAGTTGAATAT

SEQ ID NO (1)	Sequence	No Assigned in Example 3
182 1354	TTGATAATGTTTGTGTTGTGTTGTAG	28
183 1355	TGAAGAAGAAAGTATAATGATGAA	
184 1356	GTAGATTAGTTTGAAGTGAATAAT	32
185 1357	TATAGTAGTGAAGATGATATATGA	
186 1358	TATAATGAGTTGTTAGATATGTTG	
187 1359	GTTGTGAAATTAGATGTGAAATAT	
188 1360	TAATGTTGTGAATAATGTAGAAAG	40
189 1361	GTTTATAGTGAAATATGAAGATAG	42
190 1362	ATTATGAAGTAAGTTAATGAGAAG	47
191 1363	GATGAAAGTAATGTTTATTGTGAA	
192 1364	ATTATTGAGATGTGAAGTTTGT	48
193 1365	TGTAGAAGATGAGATGTATAATTA	53
194 1366	TAATTTGAGTTGTGTATATAGTAG	
195 1367	TGATATTAGTAAGAAGTTGAATAG	
196 1368	GTTAGTTATTGAGAAGTGTATATA	55
197 1369	GTAGTAATGTTAATGAATTAGTAG	58
198 1370	GTTTGTGTTGATGTGATTGAATAAT	
199 1371	GTAAGTAGTAATTTGAATATGTAG	64
200 1372	GTTTGAAGATATGTTTGAAGTATA	
201 1373	ATGATAATTGAAGATGTAATGTTG	
202 1374	GTAGATAGTATAGTTGTAATGTTA	66
203 1375	GATGTGAATGTAATATGTTTATAG	69
204 1376	TGAAATTAGTTTGTAAGATGTGTA	74
205 1377	TGTAGTATAAAGTATATGAAGTAG	63
206 1378	ATATGTTGTTGAGTTGATAGTATA	89
207 1379	ATTATTGAGTAGAAAGATAGAAAG	94
208 1380	GTTGTTGAATATTGAATATAGTTG	
209 1381	ATGAGAAGTTAGTAATGTAAATAG	
210 1382	TGAAATGAGAAGATTAATGAGTTT	

Please insert the sequence listing provided on pages 1/368 to 368/368 in the accompanying Response to the Notice to File Missing Parts of June 21, 2004, and submitted under separate cover, into the disclosure.